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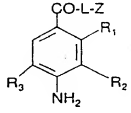
(54) Title: AZABICYCLIC AMIDES OR ESTERS OF HALOGENATED BENZOIC ACIDS



(I)

(57) Abstract

Compounds of formula (I) wherein Z is a di-azacyclic or azabicyclic side chain having 5-HT_3 receptor antagonist activity.

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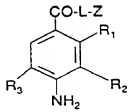
AZABICYCLIC AMIDES OR ESTERS OF HALOGENATED BENZOIC ACIDS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and their use as pharmaceuticals.

EP-A-220011 (Beecham Group p.l.c.) describes the use of a benzamide derivative, as a 5-HT_3 receptor antagonist.

A group of novel compounds has now been discovered, which compounds are 5-HT_3 receptor antagonists.

Accordingly, the present invention provides a compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen or C_{1-6} alkoxy;

R_2 is halo;

R_3 is halo;

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain;

having 5-HT_3 receptor antagonist activity.

Suitable examples of alkyl moieties in R_1 include methyl, ethyl, n- and iso-propyl, n-, iso-, sec- and tert-butyl.

Suitable examples of halo moieties include fluoro, chloro and bromo.

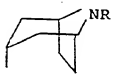
In particular, R_1 is hydrogen, R_2 is chloro and R_3 is chloro; or R_1 is methoxy, R_2 is fluoro or chloro and R_3 is chloro.

Suitable examples of Z are described in the art relating to 5-HT_3 receptor antagonists, ie. as follows:

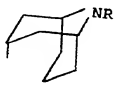
i) GB 2125398A (Sandoz Limited)
ii) GB 2152049A (Sandoz Limited)
iii) EP-A-215545 (Beecham Group p.l.c.)
iv) EP-A-214772 (Beecham Group p.l.c.)
v) EP-A-377967 (Beecham Group p.l.c.)
vi) PCT/GB91/01629 (Beecham Group p.l.c.)
vii) EP-A-358903 (Dianippon)

Particular side chains of interest are depicted thus:

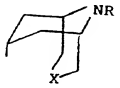
Tropane



Granatane



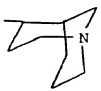
Oxa/thia-granatane



Quinuclidine

Isoquinuclidine

Isogranatane



Oxa/thia-isogranatane

Isotropane

or

wherein

R is hydrogen or methyl; and X is oxygen, sulphur or nitrogen optionally substituted by C_{1-6} alkyl, C_{3-8} cycloalkyl, C_{3-8} cycloalkyl C_{1-4} alkyl, phenyl, naphthyl, phenyl C_{1-4} alkyl or naphthyl C_{1-4} alkyl wherein a phenyl or naphthyl moiety is optionally substituted by one or more of halo, C_{1-6} alkoxy or C_{1-6} alkyl.

Side chains Z of particular interest include tropane, oxagranatane and azagranatane, where R is methyl. Suitable values for N-substituents when X is N are as described in PCT/GB91/01629, for example, iso-propyl or ethyl.

L is preferably NH.

Alternatively, COL in formula (I) may be replaced by a bioisostere therefor, for example, 1,2,4-oxadiazole and the other groups of structure h) described in EP-A-377967 (Beecham Group p.l.c.).

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

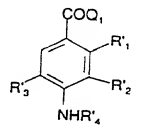
Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and n- and iso-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will of course be realised that some of the compounds of the formula (I) have chiral or prochiral centres and thus are capable of existing in a number of stereoisomeric forms including enantiomers. The invention extends to each of these stereoisomeric forms (including enantiomers), and to mixtures thereof (including racemates). The different stereoisomeric forms may be separated one from the other by the usual methods.

The invention also provides a process for the preparation of a compound of formula (I), or a pharmaceutically acceptable salt thereof, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ' (III)

or a reactive derivative thereof, when L is O;

wherein R_1', R_2', R_3' and/or Z' are R_1, R_2, R_3 and/or Z respectively or groups or atoms convertible thereto; R_4 is hydrogen or an N-protecting group; Q_1 is a leaving group; and the remaining variables are as hereinbefore defined; and thereafter optionally converting R_1', R_2', R_3' and/or Z' to another group or atom R_1, R_2, R_3 or Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

Examples of R_4, when other than hydrogen, include C_{1-10} acyl such as C_{1-7} alkanoyl, wherein the alkyl may be as listed for R_1, preferably acetyl.
R_4 is usually hydrogen.

Examples of leaving groups Q_1, displaceable by a nucleophile, include halogen such as chloro and bromo, hydroxy, C_{1-4} alkoxy, such as CH_3O and C_2H_5O-, PhO-, activated hydrocarbyloxy, such as Cl_5C_6O- or Cl_3CO-; or COQ_1, forms a mixed anhydride, so that Q_1 is carboxylic acyloxy; or a nitrogen-linked heterocycle, such as imidazole.

If a group Q_1 is a halide, or COQ_1, forms a mixed anhydride, then the reaction is preferably carried out at non-extreme temperatures in an inert non-hydroxylic solvent, such as benzene, dichloromethane, toluene, diethyl ether, tetrahydrofuran (THF) or dimethylformamide (DMF). It is also preferably carried out in the presence of an acid acceptor, such as an organic base, in particular a tertiary amine, such as triethylamine, trimethylamine, pyridine or

picoline, some of which can also function as the solvent. Alternatively, the acid acceptor can be inorganic, such as calcium carbonate, sodium carbonate or potassium carbonate. Temperatures of 0°-100°C, in particular 10-80°C are suitable.

If a group Q_1 is C_{1-4} alkoxy, phenoxy or activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as toluene or dimethylformamide. It is also preferred that the group Q_1 is Cl_3CO- and that the reaction is carried out in toluene at reflux temperature.

If a group Q_1 is hydroxy, then the reaction is generally carried out in an inert non-hydroxylic solvent, such as dichloromethane, THF or DMF optionally in the presence of a dehydrating agent such as a carbodiimide, for example dicyclohexylcarbodiimide. The reaction may be carried out at any non-extreme temperature, such as -10 to 100°C, for example, 0 to 80°C. Generally, higher reaction temperatures are employed with less active compounds whereas lower temperatures are employed with the more active compounds.

If a group Q_1 is carboxylic acyloxy, then the reaction is preferably carried in substantially the same manner as the reaction when Q_1 is halide. Suitable examples of acyloxy leaving groups include C_{1-4} alkanoyloxy and C_{1-4} alkoxycarbonyloxy, in which case the reaction is preferably carried out in an inert solvent, such as dichloromethane, at a non-extreme temperature for example ambient temperatures in the presence of an acid acceptor, such as triethylamine. C_{1-4} alkoxycarbonyloxy leaving groups may be generated <u>in situ</u> by treatment of the corresponding compound wherein Q_1 is hydroxy with a C_{1-4} alkyl chloroformate.

If a group Q_1 is activated hydrocarbyloxy then the reaction is preferably carried out in an inert polar solvent, such as dimethylformamide. It is also preferred that the activated hydrocarbyloxy group is a pentachlorophenyl ester and that the reaction is carried out at ambient temperature.

When Y is O the compound of formula (III) may be in the form of a reactive derivative thereof, which is often a salt, such as the lithium, sodium or potassium salt.

An R_2' or R_3' group which is convertible R_2 or R_3 include a hydrogen substituent which is convertible to a halogen substituent by halogenation using conventional halogenating agents.

Z' when other than Z may be wherein R is replaced by R' which is a hydrogenolysable protecting group which is benzyl optionally substituted by one or two groups selected from halo, C_{1-4} alkoxy and C_{1-4} alkyl. Such benzyl groups may, for example, be removed, when R_1/R_2 is not halogen, by conventional transition metal catalysed hydrogenolysis to give compounds of the formula (I) wherein R is hydrogen.

This invention also provides a further process for the preparation of a compound of the formula (I) wherein R is methyl or a pharmaceutically acceptable salt thereof, which comprises N-methylating a compound of formula (I) wherein R is hydrogen, and optionally forming a pharmaceutically acceptable salt of the resulting compound of the formula (I). In this further process of the invention 'N-methylation' may be achieved by reaction with a compound CH_3Q_2 wherein Q_2 is a leaving group.

Suitable values for Q_2 include groups displaced by nucleophils such as Cl, Br, I, OSO_2CH_3 or $OSO_2C_6H_4pCH_3$,

preferably Cl, Br or I.

The reaction may be carried out under conventional alkylation conditions for example in an inert solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate. Generally the reaction is carried out at non-extreme temperature such as at ambient or slightly above.

Alternatively, 'N-methylation' may be effected under conventional reductive alkylation conditions.

Interconverting R in the compound of the formula (III) before coupling with the compound of the formula (II) is also possible. Such interconversions are effected conveniently under the above conditions. It is desirable to protect any amine function with a group readily removable by acidolysis such as a C_{2-7} alkanoyl group, before R/Z interconversion.

It is often convenient in the preparation of such a compound of formula (III) to prepare the corresponding compound wherein the methyl group is replaced by alkoxycarbonyl. Such compounds may then be reduced using a strong reductant such as lithium aluminium hydride to the corresponding compound of formula (II).

The benzoic acid derivative intermediates of formula (II) are known or are preparable analogously to, or routinely from, known compounds. When R_2 is fluoro, the intermediate may be prepared by fluorination of the corresponding R_2 is hydrogen compound, using a suitable fluorinating catalyst, such as trifluoromethyl hypofluorite, as described in Description 1 hereinafter.

Compounds of the formula (III) are generally prepared from the corresponding exocyclic keto derivative of the

azabicyclic side chain, prepared by condensation methods, often using a substituted piperidine. They may be prepared by processes described in the aforementioned Patent Publications relating to values of the side chain Z.

It will be realised that in the compounds of the formula (I) having a tropane, granatane or oxa/thia/aza-granatane side chain, the -COL- linkage has an **endo** orientation with respect to the ring of the bicyclic moiety to which it is attached. A mixture of **endo** and **exo** isomers of the compound of the formula (I) may be synthesised non-stereospecifically and the desired isomer separated conventionally therefrom e.g. by chromatography; or alternatively the **endo** isomer may if desired by synthesised from the corresponding **endo** form of the compound of the formula (II). Corresponding geometric isomeric pairs are possible for the isoquinuclidine, isogranatane, oxa/thia-isogranatane and isotropane side chains.

Pharmaceutically acceptable salts of the compounds of this invention may be formed conventionally.

The salts may be formed for example by reaction of the base compound of formula (I) with a pharmaceutically acceptable organic or inorganic acid.

The compounds of the present invention are 5-HT_3 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of pain, emesis, CNS disorders and gastrointestinal disorders. Pain includes migraine, cluster headache, trigeminal neuralgia and visceral pain; emesis, includes, in particular, that of preventing vomiting and nausea associated with cancer therapy, post-operative emesis, and nausea associated with migraine. Examples of such cancer therapy include that using cytotoxic agents, such as platinum complexes including cisplatin, and also

doxorubicin and cyclophosphamide, particularly cisplatin; and also radiation treatment. CNS disorders include anxiety, psychosis, cognitive disorders such as senile dementia and age associated memory impairment (AAMI), and drug dependence. Gastrointestinal disorders include irritable bowel syndrome and diarrohea.

5-HT_3 receptor antagonists may also be of potential use in the treatment of obesity, arrhythmia, and/or disorders associated with myocardial instability.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch

derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course,

conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders herein- before described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more

than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

The following Examples illustrate the preparation of compounds of formula (I).

Examples

Ex. No.	R_1	R_2	R_3	L	Z
1	H	Cl	Cl	NH	NmT
2	H	Cl	Cl	NH	Q
3	OCH_3	Cl	Cl	NH	NmT
4	OCH_3	Cl	Cl	NH	NmO
5	OCH_3	F	Cl	NH	NmT

NmT = N-methyltropane
Q = Quinuclidin-3-yl
NmO = N-methyloxagranatane

Description

a) Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate

Methyl-4-acetamido-5-chloro-2-methoxy benzoate (10.9g) was dissolved in chloroform (40 ml), cooled to -10°C under nitrogen. A three molar excess of trifluoromethyl hypofluorite was slowly bubbled through the stirred, cooled solution for 6 hours. A slow positive nitrogen stream was maintained throughout the reaction. After warming to room temperature and thoroughly purging with nitrogen, the chloroform was removed **in vacuo**.

The residue was chromatographed on silica using chloroform with increasing amounts of methanol as eluant. The product was isolated as an off white solid.

^1H NMR ($CDCl_3$) 250MHz

δ: 7.64 (d, 1H), 7.37 (bs, 1H), 3.98 (bs, 3H), 3.9 (s, 3H), 2.2 (s, 3H)

b) 4-Amino-5-chloro-3-fluoro-2-methoxybenzoic acid

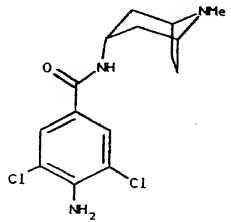
Methyl-4-acetamido-5-chloro-3-fluoro-2-methoxybenzoate (1.89g) in 25 ml ethanol was treated with a solution of sodium hydroxide (1.15g) in 15 ml water. The mixture was heated under reflux for 16 hours then cooled. The solvent was removed in vacuo and the residue acidified. The precipitated solid was collected by filtration to give 1.48g product.

^1H NMR (DMSO) 250MHz

δ: 7.49 (d, 1H), 6.19 (bs, 1H), 3.80 (s, 3H)

Example 1

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichlorobenzamide (E1)



To a stirred solution of 4-amino-3,5-dichlorobenzoic acid (1.1g) in CH_2Cl_2 (50 ml) and Et_3N (0.8 ml) at 0°C was added EtO_2CCl (0.48 ml). After stirring to room temperature for 1h, a solution of the **endo**-8-methyl-8-azabicyclo[3.2.1]octan-3-amine (0.7 g) in CH_2Cl_2 (10 ml) was added and the whole stirred overnight. The reaction mixture was washed with sat. $NaHCO_3$ solution, dried and evaporated. Recrystallisation of the residue (EtoAc/petrol) gave the title compound (0.35 g) mp 192-193°C.

^1H NMR ($CDCl_3$) δ 7.55 (s, 2H)
6.25 (brd 1H)
4.76 (brs, 2H)
4.22 (q, 1H)
3.21 (brs, 2H)
2.33 (s, 3H)
2.35-2.10 (m, 4H)
1.88-1.68 (m, 4H)

Prepared similarly was:

Example 2

N-(1-Azabicyclo[2.2.2]octan-3-yl)-4-amino-3,5-dichlorobenzamide (E2)

mp 233-235°C.

Example 3

endo-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichloro-2-methoxybenzamide (E3)

A solution of **endo**-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-5-chloro-2-methoxybenzamide (0.8g) in CH_3COOH (25 mL) was treated with a solution of Cl_2 (0.18 g) in CH_3COOH (5 mL). After standing at room temperature overnight, the solvent was removed by rotary evaporation and the residue partitioned between EtOAc and aqueous $NaHCO_3$ solution. The organic extract was separated, dried (K_2CO_3) evaporated and the residue purified by flash chromatography (SiO_2, 5-10% MeOH/$CHCl_3$) to give the title compound (0.065 g) mp 148-151°C.

Prepared similarly was:

Example 4

endo-N-(9-Methyl-9-aza-3-azabicyclo[3.3.1]nonan-7-yl)-4-amino-3,5-dichloro-2-methoxybenzamide (E4)

mp 170-172°C.

Example 5

endo-4-Amino-5-chloro-3-fluoro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)benzamide (E5)

The title compound was prepared from 4-amino-5-chloro-3-fluoro-2-methoxybenzoic acid via an analagous procedure to that described for Example 1.

The product was isolated as the hydrochloride salt, mp 202-203°C.

^{1}H NMR (free base), ($CDCl_3$), 250 MHz

δ: 8.61 (bd, 1H), 7.81 (d, 1H), 4.34 (bs, 2H), 4.20 (dd, 1H), 3.98 (d, 3H), 3.10 (b, 2H), 1.53-2.21 (m, 11H inc.s, 2.21, 3H).

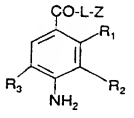
5-HT_3 Receptor Antagonist Activity

Compounds are evaluated for antagonism of the von Bezold-Jarisch reflex evoked by 5-HT in the anaesthetised rat according to the following method:

Male rats 250-350g, are anaesthetised with urethane (1.25g/kg intraperitoneally) and blood pressure and heart rate are recorded as described by Fozard J.R. et al., J. Cardiovasc. Pharmacol. 2, 229-245 (1980). A submaximal dose of 5-HT (usually 6μg/kg) is given repeatedly by the intravenous route and changes in heart rate quantified. Compounds are given intravenously and the concentration required to reduce the 5-HT-evoked response to 50% of the control response (ED_{50}) is then determined.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof:



(I)

wherein

R_1 is hydrogen or C_{1-6} alkoxy;

R_2 is halo;

R_3 is halo;

L is O or NH; and

Z is a di-azacyclic or azabicyclic side chain;

having 5-HT_3 receptor antagonist activity.

2. A compound according to claim 1 wherein R_1 is hydrogen, R_2 is chloro and R_3 is chloro.

3. A compound according to claim 1 wherein R_1 is methoxy, R_2 is fluoro or chloro and R_3 is chloro.

4. A compound according to any one of claims 1 to 3 wherein the side chain Z is tropane, granatane, oxa/thia/aza-granatane, quinuclidine, isoquinuclidine, isogranatane, oxa/thia-isogranatane or isotropane.

5. A compound according to claim 4 wherein Z is tropane, oxagranatane or azagranatane.

6. A compound according to any one of claims 1 to 5 wherein L is NH.

7. **endo**-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichlorobenzamide.

8. N-(1-Azabicyclo[2.2.2]octan-3-yl)-4-amino-3,5-dichlorobenzamide.

9. **endo**-N-(8-Methyl-8-azabicyclo[3.2.1]octan-3-yl)-4-amino-3,5-dichloro-2-methoxybenzamide.

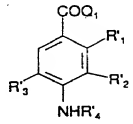
10. **endo**-N-(9-Methyl-9-aza-3-azabicyclo[3.3.1]nonan-7-yl)-4-amino-3,5-dichloro-2-methoxybenzamide.

11. **endo**-4-Amino-5-chloro-3-fluoro-2-methoxy-N-(8-methyl-8-azabicyclo[3.2.1.]octan-3-yl)benzamide.

12. A pharmaceutically acceptable salt of a compound according to any one of claims 7 to 11.

13. A compound according to claim 1 substantially as defined herein with reference to the Examples.

14. A process for the preparation of a compound according to claim 1, which process comprises reacting a compound of formula (II):



(II)

with a compound of formula (III):

HLZ' (III)

or a reactive derivative thereof, when L is O;

wherein R_1', R_2', R_3' and/or Z' are R_1, R_2, R_3 and/or Z respectively or groups or atoms convertible thereto; R_4 is hydrogen or an N-protecting group; Q_1 is a leaving group; and the remaining variables are as defined in claim 1; and thereafter optionally converting R_1', R_2', R_3' and/or Z' to another group or atom R_1, R_2, R_3 or Z; and optionally forming a pharmaceutically acceptable salt of the resultant compound of formula (I).

15. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutically acceptable carrier.

16. A method of treatment or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders in mammals, such as humans, which comprises the administration of an effective amount of a compound according to claim 1.

17. A compound according to any one of claims 1 to 13 for use as an active therapeutic substance.

18. A compound according to any one of claims 1 to 13 for use in the treatment of pain, emesis, CNS disorders and/or gastrointestinal disorders.

19. The use of a compound according to any one of claims 1 to 13 in the manufacture of a medicament for the treatment and/or prophylaxis of pain, emesis, CNS disorders and/or gastrointestinal disorders.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 91/02210

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[5]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC5: C 07 D 451/04, 453/02, 498/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
IPC5	C 07 D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category *	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP, A2, 0220011 (BEECHAM GROUP PLC) 29 April 1987, see compound 20	1-15,17-19
X	EP, A2, 0377967 (BEECHAM GROUP PLC) 18 July 1990, see example 2	1-15,17-19
X	EP, A1, 0099789 (DELALANDE S.A.) 1 February 1984, see especially compound 24	1-15,17-19

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
10th March 1992	6 APR 1992
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Mireille Meinhold

Form PCT/ISA/210 (second sheet) (January 1985)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	DE, DE, 3001328 (DELALANDE S.A.) 24 July 1980, see example 74	1,4,14-15,17-19

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [ ] Claim numbers ..... 16, because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1 (iv: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [X] Claim numbers ..... 1-4* because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The scope of the claims 1-4, 14-15, 17-19 is so broadly formulated that a very wide range of structures is included. These claims have thus not been fully searched.

* 14-15, 17-19

3. [ ] Claim numbers ....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. PCT/GB 91/02210

SA 53948

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 01/02/92
The European Patent office is in no way liable for theseparticulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A2- 0220011	29/04/87	AU-D-	6385586	16/04/87
		JP-A-	62155277	10/07/87
EP-A2- 0377967	18/07/90	AU-D-	4608189	21/06/90
		JP-A-	2202890	10/08/90
EP-A1- 0099789	01/02/84	AU-B-	562210	04/06/87
		AU-D-	1650783	05/01/84
		CA-A-	1265802	13/02/90
		FR-A-B-	2529548	06/01/84
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		BE-A-	881134	14/07/80
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		FR-A-B-	2476088	21/08/81
		GB-A-B-	2042522	24/09/80
		GB-A-B-	2055374	04/03/81
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		US-A-	4536580	20/08/85